Long-term recurrence rate of large and difficult to treat cutaneous squamous cell carcinomas after superficial radiotherapy

Barysch, M J ; Eggmann, N ; Beyeler, M ; Panizzon, R G ; Seifert, Burkhardt ; Dummer, R

Abstract: Background: Surgical excision is the gold standard for cutaneous squamous cell carcinoma (cSCC), however its application is limited in specific cases. Superficial radiotherapy (RTx)is an alternative treatment option, but long-term follow-up data are limited. Objective: To determine the outcome of superficial RTx of cSCC in correlation to histological differentiation grade and tumor localization. Methods: The outcome of 180 large cSCCs after superficial RTx between 1960 and 2004 was retrospectively reviewed. Results: Mean tumor size was 3.5 cm 2 (SD 7.5) and mean follow-up period was 4.9 years (SD 4.7). Relapse-free survival was 95.8 and 80.4% after 1 and 10 years. Two-year relapse-free survival was 94.8% for good, 88.9% for moderate and 85.7% for poor differentiated tumors. Five-year relapse-free survival was highest in cSCCs located around the eyes (100%) and cheeks (90.9%). Conclusion: Superficial RTx is an effective alternative for cSCC if surgery is difficult due to localization or concomitant disease.

DOI: https://doi.org/10.1159/000337027

Original Paper

Dermatology

Dermatology
DOI: 10.1159/000337027

Received: June 24, 2011
Accepted after revision: January 31, 2012
Published online: March 20, 2012

Long-Term Recurrence Rate of Large and Difficult to Treat Cutaneous Squamous Cell Carcinomas after Superficial Radiotherapy

Marjam J. Barysch[a] Nina Eggmann[a] Mirjam Beyeler[b] Renato G. Panizzon[c] Burkhardt Seifert[d] Reinhard Dummer[a]

[a]Department of Dermatology, University Hospital Zurich, Zurich, [b]Dermatological Practice Altenburg, Wettingen, [c]Department of Dermatology, University Hospital Lausanne, Lausanne, and [d]Biostatistics Unit, Institute for Social and Preventive Medicine, University of Zurich, Zurich, Switzerland

Key Words
Cutaneous squamous cell carcinoma · Non-melanoma skin cancer · Superficial radiotherapy · Recurrence rates

Abstract
Background: Surgical excision is the gold standard for cutaneous squamous cell carcinoma (cSCC), however its application is limited in specific cases. Superficial radiotherapy (RTx) is an alternative treatment option, but long-term follow-up data are limited. ***Objective:*** To determine the outcome of superficial RTx of cSCC in correlation to histological differentiation grade and tumor localization. ***Methods:*** The outcome of 180 large cSCCs after superficial RTx between 1960 and 2004 was retrospectively reviewed. ***Results:*** Mean tumor size was 3.5 cm^2 (SD 7.5) and mean follow-up period was 4.9 years (SD 4.7). Relapse-free survival was 95.8 and 80.4% after 1 and 10 years. Two-year relapse-free survival was 94.8% for good, 88.9% for moderate and 85.7% for poor differentiated tumors. Five-year relapse-free survival was highest in cSCCs located around the eyes (100%) and cheeks (90.9%). ***Conclusion:*** Superficial RTx is an effective alternative for cSCC if surgery is difficult due to localization or concomitant disease.

Marjam J. Barysch and Nina Eggmann contributed equally to this work.

Introduction

Cutaneous squamous cell carcinoma (cSCC) is a common skin cancer with an incidence rate of 12–29/100,000/year in Europe and 700/100,000/year in Australia [1–7]. Populations with fair skin that experience high cumulative UV exposure are at highest risk for cSCC development, sun-exposed areas being majorly affected [8–10].

The treatment of choice for invasive cSCC is surgery, particularly Mohs micrographic surgery [11–16] producing the lowest recurrence rates. In elderly patients with problematic co-morbidities and critical tumor localizations, radiotherapy (RTx) can be an alternative option [11–26], but reports of superficial RTx and data on long-term outcome are limited [17, 19–20, 22].

In the following, relapse rates of cSCCs after superficial RTx are reported from a retrospective study. Data are correlated with the tumors' histological differentiation and anatomical distribution.

Patients and Methods

The present retrospective study included all patients with cSCCs who were treated with superficial RTx at the Department of Dermatology, University Hospital of Zurich, Switzerland during 1960–2004. The patients were treated with Dermax 4000 following standard guidelines if surgical excision was not favored by

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1018–8665/12/0000–0000$38.00/0

Accessible online at:
www.karger.com/drm

Prof. Dr. med. Reinhard Dummer
Department of Dermatology, University Hospital Zurich
Gloriastrasse 31
CH–8091 Zurich (Switzerland)
Tel. +41 44 255 2507, E-Mail reinhard.dummer@usz.ch

Table 1. Patient characteristics

Sex		Age, years (mean ± SD)	Treated cSCC		Histological differentiation			Tumor localization				
			primary	relapsed	good	moderate	poor	head and neck	trunk	upper extremities	lower extremities	genital
Male	113 (114 lesions)	67.2 ± 13.9	111	3	57	26	9	103 (90.4%)	1 (0.9%)	6 (5.3%)	3 (2.6%)	1 (0.9%)
Female	66	71.7 ± 12.0	66	0	41	7	7	53 (80.3%)	0 (0.0%)	10 (15.2%)	2 (3.0%)	1 (1.5%)
Total	179 (180 lesions)	69.5	177	3	98	33	16	156 (87%)	1 (0.6%)	16 (8.9%)	5 (2.8%)	2 (1.2%)

One male patient had 2 lesions. Percentages apply to lesions per gender.

Table 2. Tumor localization of the head and neck

	Eye	Scalp	Lips	Nose	Ear	Front	Cheek
Male	2 (1.9%)	11 (10.7%)	28 (27.2%)	14 (13.6%)	21 (20.4%)	17 (16.5%)	10 (9.7%)
Female	8 (15.1%)	3 (5.7%)	12 (22.6%)	11 (20.8%)	3 (5.7%)	9 (17.0%)	7 (13.2%)
Total	10 (6.4%)	14 (9.0%)	40 (25.6%)	25 (16.0%)	24 (15.4%)	26 (16.7%)	17 (10.9%)

Percentages apply to lesions per gender.

the patients (mostly due to the patient's co-morbidities combined with tumor size and localization). The decision to treat with RTx instead of surgery was individually taken by the physician together with the patient. Overall, patients were offered treatment with superficial RTx if they were of high age and presented a lesion of large size or localized at difficult sites. Patients who were lost to follow-up were sent a new appointment for consultation. Patients treated after 2004 were not included in the study in order to keep a standard as the equipment changed afterwards.

The diagnoses were histologically confirmed by H&E staining prior to treatment. Lesion size was measured by multiplying the two largest diameters that were perpendicular to each other. Superficial RTx was performed using Dermax 4000, a beryllium-windowed soft X-ray machine (R. Liechti AG, Kriegstetten, Switzerland) using 10, 20, 30, 40 or 50 kV. A field margin of 1 cm to the clinical tumor edges was applied. The administered electric potential ranged from 30 to 60 kV. Depending on the thickness of the interposed aluminum filter (0.5–2.0 cm), the electric current (20 mA), the focus-skin distance (3–20 cm) and the resulting half value layer (4–15 mm) varied.

Relapse rates according to the patient's age, tumor localization and histological differentiation grade (according to standard criteria [27]) were analyzed retrospectively.

Statistical Analysis

GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, Calif., USA) was used for statistical analyses. Overall and recurrence-free survival, depending on the patient's age, tumor localization and differentiation grade, was analyzed using Kaplan-Meier and Cox regression. A p value <0.05 was considered to be significant; a 95% confidence interval (CI) was computed.

Results

179 patients (66 female [37%], 113 male [63%]) with a mean age of 69 years (SD 12.93, 95% CI 61.37–66.53) were included, accounting for 180 cSCC lesions which were treated with superficial RTx during the mentioned time span. One patient was renal transplanted and received immunosuppressive medications, 4 patients suffered from diabetes mellitus, and 11 patients revealed a malignancy in their history (tables 1–3). Of the 180 lesions, 166 were primary lesions, and 4 were recurrent and completely excised before start of RTx. Most of the lesions (86.7%) were located on the head and neck. Lesions other than from the head and neck area (13.3%) were mostly located on the extremities (8.9%). Histological evaluation revealed 98 tumors (54.8%) as well, 33 (18.3%) as moderately and 15 (8.4%) as poorly differentiated. Mean tumor size was 3.5 cm^2 (SD 7.5, 95% CI 2.4–4.6) (tables 1, 2).

The lesions were treated with a mean dose fractionation of 4.6 Gy (SD 1.5, 95% CI 4.3–4.8) and a mean cumulative dose of 48.2 Gy (SD 6.6, 95% CI 47.2–49.2) during 11.4 sessions (SD 3.4, 95% CI 10.9–11.9). There was a significant correlation of tumor size and cumulative dose ($p < 0.00001$, two-tailed paired t test). A mean half value layer of 7.2 (SD 3.4, 95% CI 6.7–7.7) and a mean focus-skin distance of 15.1 cm (SD 4.6, 95% CI 14.5–15.8) were applied using a mean electric potential of 37.3 kV (SD 8.0,

95% CI 36.1–38.4) and a mean electric current of 11.0 mA (SD 3.2, 95% CI 10.5–11.5) (table 4).

Follow-up visits were attended for more than 1 year in 136 patients (75.6%); 69 patients attended for more than 5 years (38.3%), and 23 (12.8%) for more than 10 years (visits every 6 months). The mean follow-up period was 4.9 years (SD 4.7; 95% CI 4.2–5.6).

Relapses and Overall Relapse-Free Survival

Of the 180 lesions, 24 relapses (13%) were registered with a mean delay of 2.7 years (SD 2.98, 95% CI 1.40–3.92) after start of superficial RTx. One of these lesions revealed lymph node infiltration 1.7 years after treatment. All relapsed cSCCs were originally primary tumors before treated with superficial RTx. Except for 1 case which was located on the lower limbs, all relapsed cSCCs originated from the head and neck area, all deriving from primary tumors. Unfortunately, information about the accurate localization of the relapses within the radiated area (center versus edge) is not retraceable retrospectively. Apart from two cases – one patient with colon cancer, one with chronic lymphatic leukemia – there is no evidence for immunodeficiency in the patients who experienced a relapse (table 3). The risk for relapses after RTx increased significantly with age ($p = 0.012$) and correlated significantly with tumor size ($p > 0.0001$, Cox regression). The overall relapse-free survival 1, 2, 5 and 10 years after superficial RTx was 95.8, 91.5, 86.2 and 80.4%, respectively (fig. 1).

Relapse-Free Survival and Histological Differentiation Grade

Histological differentiation grade is known in 81.7% ($n = 147$). Tumor size and histological differentiation correlated significantly ($p < 0.0011$, two-tailed paired t test). Of these lesions, well differentiated ones relapsed in 11.2% (11/98), moderately differentiated ones in 15.2% (5/33) and poorly differentiated ones in 25% (4/16). The number of cases is too small to reach a significant level, however there is a trend for a better outcome for well differentiated cSCCs ($p = 0.1$). Relapse-free survival after 1, 2, 5 and 10 years was 97.4, 94.8, 89.3 and 82.1% in well differentiated tumors, 96.3, 88.9, 80.7 and 80.7% in moderately differentiated tumors, and 92.9, 85.7, 77.9 and 39.0% in poorly differentiated tumors (table 5; fig. 1, 2).

Relapse-Free Survival and Tumor Localization

The number of tumor sites other than the head and neck was too small to perform further differentiation. Concerning the head and neck area, the distinguished sites were classified as areas around the ears, eyes, nose, lips, cheeks, scalp, forehead and neck. cSCCs around/at the ears and scalp presented significantly higher relapse rates ($p = 0.025$) compared to other sites: five-year relapse-free survival was 69.2% for tumors on the scalp, 72.2% for tumors around the ears, while lesions around the eyes and cheeks revealed 100 and 90.9% five-year relapse-free survival. Tumors located on the remaining body parts other than the head and neck area were mostly located on the extremities and showed relapse-free survival of 94.7% at 5 years (tables 1, 2, 6). Figure 3 illustrates 3 clinical examples before treatment and clinical outcome after treatment. Figure 4 shows the histology of an SCC (Bowen carcinoma) before and after treatment.

Table 3. Immunosuppressive disorders and relapses

Diagnosis	Cases	Relapses
Renal transplant recipient	1	0
Prostate cancer	2	0
Breast cancer	4	0
Colon cancer	1	1
Chronic lymphatic leukemia	2	1
Waldenström's macroglobulinemia	1	0
Non-Hodgkin lymphoma and colon carcinoma	1	0
Diabetes mellitus	4	0

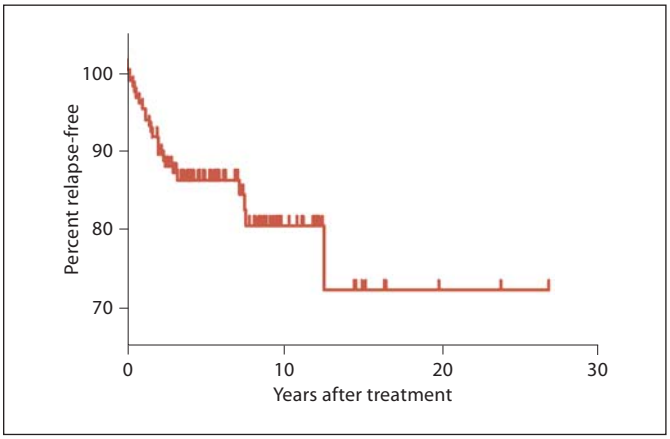


Fig. 1. Overall relapse-free survival. Number of patients at endpoint: 157.

Discussion

For the treatment of superficial cSCCs, different treatment modalities have been approved [11, 16, 25], while for invasive cSCCs nowadays standard treatment is sur-

Table 4. Applied cumulative dose and corresponding lesion size, applied dose fractionation, focus-skin distance, number of treatments, half value layer and electric potential

Cumulative dose, Gy	Cases, n	Lesion size, cm	Dose fractionation, Gy	Focus-skin distance, cm	Number of treatments	Half value layer	Electric potential, kV
20	2	11.4 ± 15.4	4 ± 0	11.5 ± 45	21.2 ± 12.0	9 ± 5.7	9.5 ± 7.8
24	1	2.5 ± 0.0	4 ± 0	20 ± 20	0 ± 0	6 ± 0	2.6 ± 0
28	1	0.2 ± 0.0	4 ± 0	20 ± 30	0 ± 0	7 ± 0	4 ± 0
32	2	0.4 ± 0.1	8 ± 0	9.0 ± 25	7.1 ± 4.2	4 ± 0	3.3 ± 1
36	3	0.4 ± 0.3	4 ± 0	17.3 ± 30	0 ± 4.6	8.7 ± 0.6	14 ± 0
40	14	6.3 ± 18.4	5.1 ± 2.7	13.4 ± 35	12.9 ± 6.6	9.1 ± 4.2	6.4 ± 4.2
42	2	0.6 ± 0.0	5 ± 1.4	8.5 ± 50	14.1 ± 5.0	8.5 ± 2.1	11.6 ± 4.9
44	15	2.9 ± 6.0	4 ± 0	14.4 ± 32.7	4.6 ± 4.2	11 ± 0	5.1 ± 1.9
46	1	0.8 ± 0.0	6 ± 0	12 ± 30	0 ± 0	8 ± 0	4 ± 0
48	84	4.2 ± 6.7	4.6 ± 1.5	15.8 ± 37	6.2 ± 4.4	11.2 ± 2.6	7 ± 2.7
50	1	0.3 ± 0.0	4 ± 0	12 ± 30	0 ± 0	12 ± 0	4 ± 0
52	15	1.5 ± 1.5	4 ± 0	15.2 ± 35	6.4 ± 4.1	13 ± 0	6.3 ± 2.8
54	6	4.4 ± 8.4	4.3 ± 1.5	14.7 ± 40	6.3 ± 4.1	14 ± 7	8.5 ± 3.3
56	27	2.2 ± 2.8	4.9 ± 1.7	15.1 ± 42.6	7.1 ± 3.9	12.4 ± 3	9.8 ± 3.6
58	1	3.0 ± 0.0	2 ± 0	20 ± 40	0 ± 0	29 ± 0	8.1 ± 0
60	3	4.2 ± 6.3	4 ± 0	14.7 ± 4.3	5.8 ± 4.6	15 ± 0	9.8 ± 3
61	1	0.4 ± 0.0	3 ± 0	20 ± 50	0 ± 0	22 ± 0	14.3 ± 0
64	1		4 ± 0	12 ± 40	0 ± 0	10 ± 0	8.1 ± 0

Figures are mean ± SD unless indicated otherwise.

Table 5. Relapse-free survival after 1, 2, 5 and 10 years in correlation to histological differentiation grade

Histological differentiation	1 year	2 years	5 years	10 years
Good	97.4%	94.8%	89.3%	82.1%
Moderate	96.3%	88.9%	80.7%	80.7%
Poor	92.9%	85.7%	77.9%	39.0%

Table 6. Tumor site and relapse-free survival after 1, 2 and 5 years

Localization	Cases	1 year	2 years	5 years
Eye	10 (5.6%)	100%	100%	100%
Scalp	14 (7.8%)	92.3%	84.6%	69.2%
Lips	40 (22.2%)	87.4%	87.4%	83.6%
Nose	25 (13.9%)	100%	100%	95.2%
Ear	24 (13.3%)	88.9%	77.8%	72.2%
Forehead	26 (14.4%)	100%	94.4%	87.7%
Cheek	17 (9.4%)	100%	100%	90.9%
Others than HN	24 (13.3%)	100%	94.7%	94.7%

HN = Head and neck.

gery. Mohs micrographic surgery improves relapse-free survival with relapse rates of 1.2–3.5% after 1.5–4 years [13–14, 28], but direct comparison of Mohs micrographic surgery to RTx should be performed with caution due to inclusion bias. Evaluating larger cSCCs measuring >2 cm in diameter which were treated with Mohs micrographic surgery, much higher recurrence rates of 25% were recorded [29]. Besides, radical excision of large cSCCs or cSCCs localized at difficult sites may lead to functional and cosmetic complications with the risk of mutilations and dysfunctions. Also for patients of advanced age who present multiple co-morbidities, wide excision – even if tumescent anesthesia is used – may be detrimental, and often hospitalization is required in this patient group [13].

Other skin tumors are effectively treated with superficial RTx – basal cell carcinoma with a recurrence rate of 16% after 5 years, and lentigo maligna and lentigo maligna melanoma with 7% after 8 years as studies showed in the past [30, 31]. For specific cases, RTx can be superior to surgery concerning cosmesis and functional results [22, 32] even in view of possible late adverse events [33, 34]. Taking these advantages into account, we retrospectively evaluated our data on RTx-treated cSCCs over a long time period. Further studies registered relapse

rates of 7% 6 years after superficial RTx [35] and control rates of up to 80% in another clinical trial including 142 cSCCs (data are mixed with results of electron beam therapy) [22]. Another study including 111 patients with SCC registered a 5-year cure rate of 92.7% [36].

We found relapse-free survival in 95.8, 91.5 and 86.2% of patients 1, 2 and 5 years after RTx in large cSCCs with a mean diameter of 3.5 cm^2. These data are in concordance with most previous studies, although we evaluated lesions at high risk of recurrences regarding the averaged lesion size of >2 cm, which itself has a higher recurrence rate [37]. A mean tumor size of 3.5 cm^2 alone does not necessarily imply a situation which is not feasible for surgery, but tumor localization played an additional and important role in the decision to perform superficial RTx, as did the patient's co-morbidities and the patient's choice.

We further show that differentiation into histological differentiation grades is of great importance regarding the excellent outcomes of relapse-free survival of 94.8% in well differentiated but only 85.7% in poorly differentiated tumors at 2 years. These data confirm that RTx is not recommended for poorly differentiated cSCCs, although other treatment options show high recurrence rates in these cases as well [38]. However, it has to be stated that these data only provide a trend and are not reliable in this case as already mentioned above.

We found a correlation between clinical outcome and tumor localization of the head and neck region showing the best prognosis for cSCCs of the eyes (no recurrence in 10 patients at 5 years), nose (95.2% recurrence-free) and cheeks (90.9% recurrence-free) while lesions from the scalp and ears were recurrence-free only in 69.2 and 72.2%, respectively (data refer to 5-years relapse-free survival). The underlying reason for the disparities in outcome may be suggested in the anatomical structures with a possible local invasion of the bones or cartilaginous tissue in the latter sites. Unfortunately, data about possible invasion cannot be collected retrospectively, but we did not register any metastases besides one case of cSCC from the scalp who developed lymph node metastases.

For young patients who present good surgical applicability, total excision should remain the treatment of choice. The same applies to immunocompromised patients though the low number of patients does not allow any statistically correct conclusion in this group. Patients with xeroderma pigmentosum may also profit from adjuvant RTx as case reports show normal response to RTx. Their defects in the DNA repair mechanism are believed

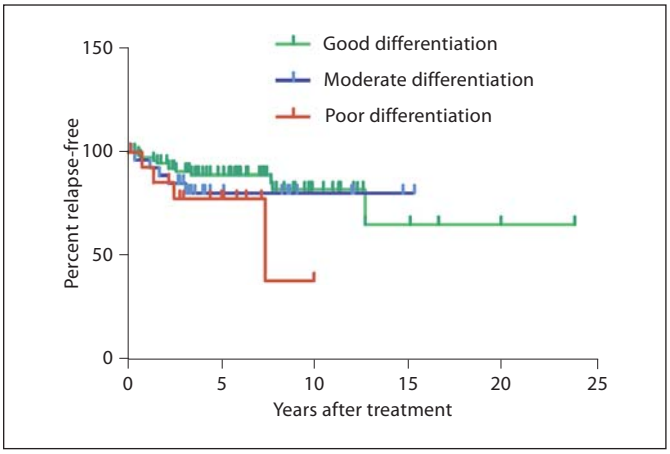


Fig. 2. Relapse-free survival depending on grade of differentiation. Number of patients at endpoint: 87 for well, 28 for moderately and 11 for poorly differentiated tumors. Number of patients at beginning: 97 for well, 33 for moderately and 15 for poorly differentiated tumors.

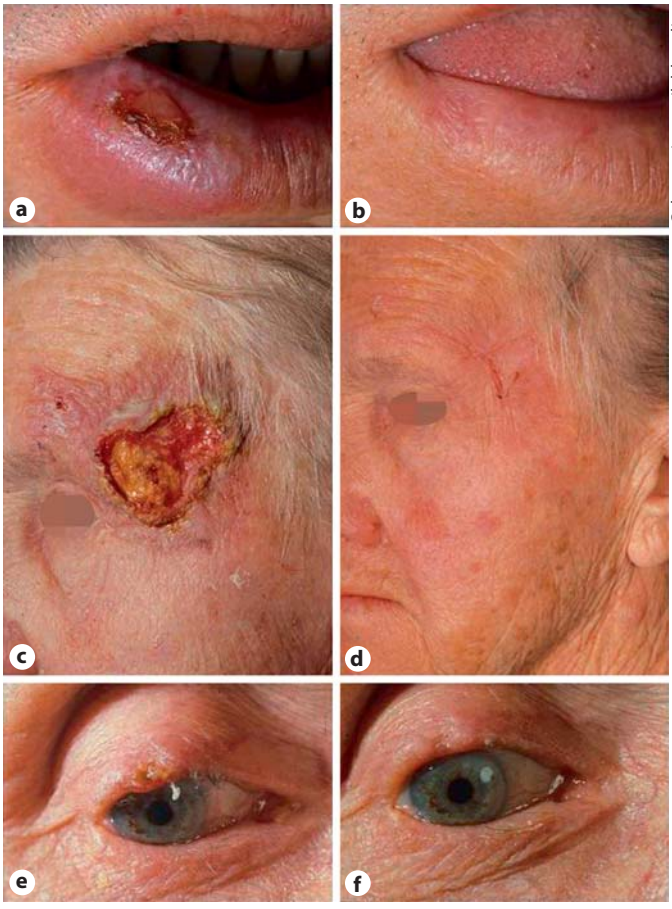
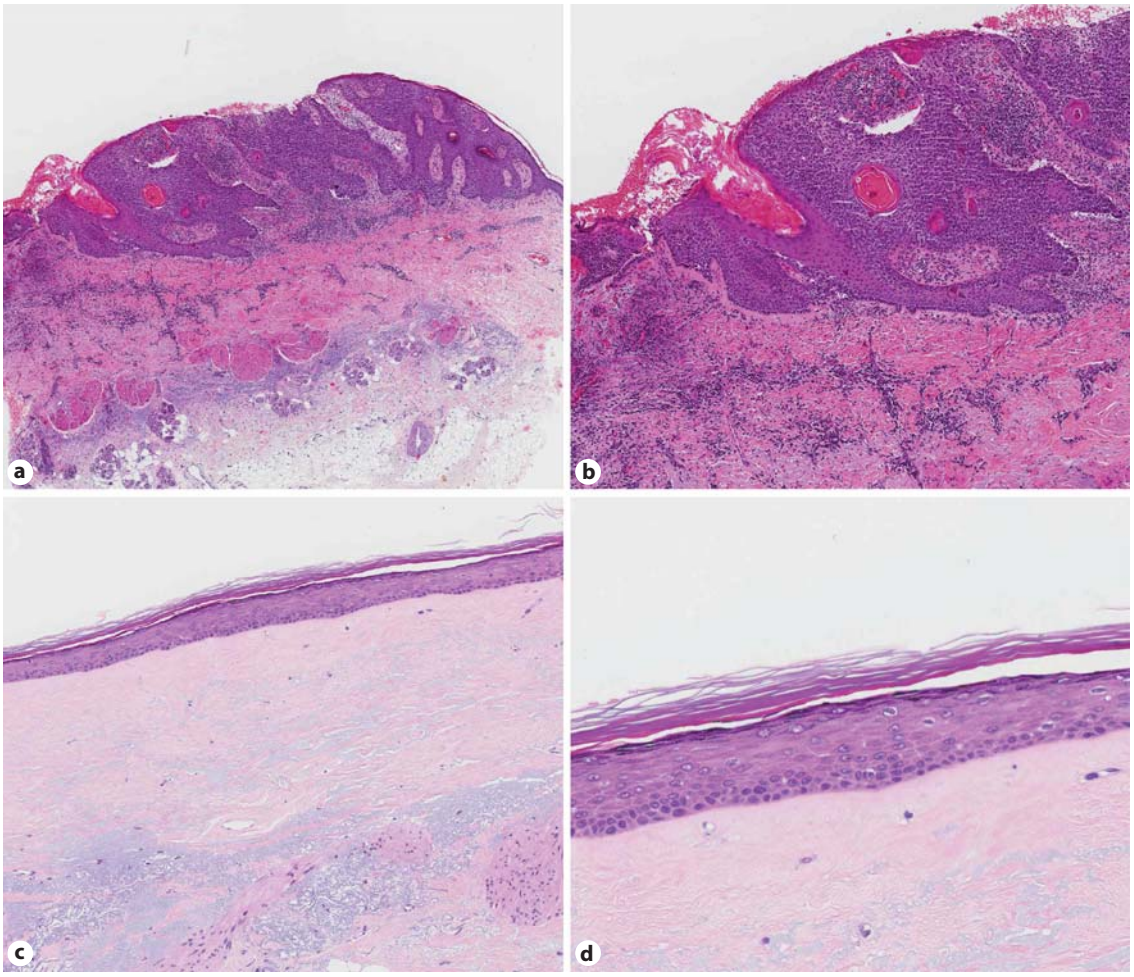


Fig. 3. cSCC of the lip before (**a**) and after treatment (**b**), of the left temple before (**c**) and after treatment (**d**), and of the eyelid before (**e**) and after treatment (**f**).



Color version available online

Fig. 4. Histology of a cSCC (Bowen carcinoma) before (**a**, **b**) and after treatment (**c**, **d**). H&E staining.

to be specifically induced by UV radiation but not by RTx [39].

A limitation of the study is the fact that information about the localization of the relapses – e.g. in-field versus at the irradiation margins – is lacking. As tumor thickness is not retraceable in the majority of cases, classification of the tumors according to the American Joint Committee on Cancer is not possible. Furthermore, patient selection was individually performed and there were no standardized inclusion criteria as this was a retrospective study. Therefore, biases in patient selection, patient referral (as this study was performed in a center) and classification are possible. Larger prospective clinical trials are required to confirm the achieved results.

Conclusion

Superficial RTx is a safe and efficient treatment option for cSCCs localized around the mouth, eyes and nose in patients for whom surgery is hardly feasible without risking considerable side effects. It is particularly favorable for elderly patients for whom surgery would be an increased health risk and if functional or cosmetic impairment is expected.

Disclosure Statement

The authors have no conflict of interest or financial support to disclose.

References

1 Buettner PG, Raasch BA: Incidence rates of skin cancer in Townsville, Australia. Int J Cancer 1998;78:587–593.
2 English DR, et al: Incidence of non-melanocytic skin cancer in Geraldton, Western Australia. Int J Cancer 1997;73:629–633.
3 Levi F, et al: Trends in skin cancer incidence in Vaud: an update, 1976–1998. Eur J Cancer Prev 2001;10:371–373.
4 de Vries, E, et al: Predictions of skin cancer incidence in the Netherlands up to 2015. Br J Dermatol 2005;152:481–488.
5 Karagas MR, et al: Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer 1999;81: 555–559.
6 Koh D, et al: Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968–97. Br J Dermatol 2003;148:1161–1166.
7 Stang A, Stegmaier C, Jockel KH: Nonmelanoma skin cancer in the Federal State of Saarland, Germany, 1995–1999. Br J Cancer 2003;89:1205–1208.
8 Hussein MR: Ultraviolet radiation and skin cancer: molecular mechanisms. J Cutan Pathol 2005;32:191–205.
9 Brash DE, et al: A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci USA 1991;88:10124–10128.
10 Mittelbronn MA, et al: Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol 1998;37: 677–681.
11 Motley R, Kersey P, Lawrence C: Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Plast Surg 2003;56: 85–91.
12 Batra RS, Kelley LC: Predictors of extensive subclinical spread in nonmelanoma skin cancer treated with Mohs micrographic surgery. Arch Dermatol 2002;138:1043–1051.
13 Breuninger H, et al: Locally infiltrative growth of squamous cell carcinoma of the skin and treatment guidelines resulting from it (in German). Hautarzt 1991;42:559–563.
14 Silapunt S, Peterson SR, Goldberg LH: Squamous cell carcinoma of the auricle and Mohs micrographic surgery. Dermatol Surg 2005; 31:1423–1427.
15 Szeimies RM, Karrer S, Backer H: Therapeutic options for epithelial skin tumors. Actinic keratoses, Bowen disease, squamous cell carcinoma, and basal cell carcinoma (in German). Hautarzt 2005;56:430–440.
16 Breuninger H, et al: Short German guidelines: squamous cell carcinoma. J Dtsch Dermatol Ges 2008;6(suppl 1):S5–S8.
17 Benasso M, et al: Gemcitabine, cisplatin, and radiation in advanced, unresectable squamous cell carcinoma of the head and neck: a feasibility study. Am J Clin Oncol 2001;24: 618–622.
18 Marmur ES, Schmults CD, Goldberg DJ: A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. Dermatol Surg 2004;30:264–271.
19 Veness M, Richards S: Role of modern radiotherapy in treating skin cancer. Australas J Dermatol 2003;44:159–166; quiz 167–168.
20 Veness MJ, et al: Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. Laryngoscope 2005;115:870–875.
21 Babilas P, et al: Photodynamic therapy in dermatology – an update. Photodermatol Photoimmunol Photomed 2005;21:142–149.
22 Locke J, et al: Radiotherapy for epithelial skin cancer. Int J Radiat Oncol Biol Phys 2001;51:748–755.
23 Dummer R, et al: Cutaneous neoplasms (in German). Praxis (Bern 1994) 2003;92:1470–1478.
24 Urosevic M, Dummer R: Role of imiquimod in skin cancer treatment. Am J Clin Dermatol 2004;5:453–458.
25 Dummer R, et al: Intralesional adenovirus-mediated interleukin-2 gene transfer for advanced solid cancers and melanoma. Mol Ther 2008;16:985–994.
26 Gille J, Spieth K, Kaufmann R: Metronomic low-dose chemotherapy as antiangiogenic therapeutic strategy for cancer. J Dtsch Dermatol Ges 2005;3:26–32.
27 LeBoit PE, Burg G, Weedon D, Sarasin A (eds): Pathology and Genetics of Skin Tumours. WHO/IARC Classification of Tumours, 2005.
28 Pugliano-Mauro M, Goldman G: Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma. Dermatol Surg 2010;36:1544–1553.
29 Rowe DE, Carroll RJ, Day CL Jr: Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 1992;26:976–990.
30 Farshad A, et al: A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. Br J Dermatol 2002;146:1042–1046.
31 Zagrodnik B, et al: Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. Cancer 2003;98:2708–2714.
32 Mendenhall WM, et al: Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. Laryngoscope 2009; 119:1994–1999.
33 Schulte KW, et al: Late adverse effects after soft X-ray therapy of cutaneous malignancies: pruritus, burning, epiphora and insufficient occlusion of the mouth. J Eur Acad Dermatol Venereol 2008;22:555–560.
34 Rupprecht R, et al: Late side-effects with cosmetic relevance following soft X-ray therapy of cutaneous neoplasias. J Eur Acad Dermatol Venereol 2007;21:178–185.
35 Schulte KW, et al: Soft x-ray therapy for cutaneous basal cell and squamous cell carcinomas. J Am Acad Dermatol 2005;53:993–1001.
36 Hernandez-Machin B, et al: Office-based radiation therapy for cutaneous carcinoma: evaluation of 710 treatments. Int J Dermatol 2007;46:453–459.
37 Mullen JT, et al: Invasive squamous cell carcinoma of the skin: defining a high-risk group. Ann Surg Oncol 2006;13:902–909.
38 Veness MJ: High-risk cutaneous squamous cell carcinoma of the head and neck. J Biomed Biotechnol 2007;2007:80572.
39 Panizzon RG, Cooper JS (eds): Radiation Treatment and Radiation Reactions in Dermatology. New York, Springer, 2004.